CERTIFICATION OF FACSIMILE TRANSMISSION

I hereby certify that this paper is being facsimile transmitted to the Patent and Trademark Office, Fax No. (703) 308-4556, on the date shown below.

R. Craig Tucker
Type or print name of person signing certification

R. Craig Tucker — February 5, 2003
Signature — Date

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	:	Krushinski et al.	)
Serial No.	:	09/890,741	)
Filed	:	December 4, 2001	) Group Art Unit: 1624
For	:	5-HT1 F AGONISTS	) Examiner: Mark L. Berch
Docket No.	:	X-11704	)

DECLARATION UNDER 37 C.F.R. § 1.132

Assistant Commissioner for Patents
Washington, D. C. 20231
Sir:

I, John Mehnert Schaus, declare that:

I hold the degree of Doctor Of Philosophy in Chemistry. I received my degree in 1980 in the Department of Chemistry at Harvard University. My Ph.D. thesis was entitled "Part I. Synthesis of Reserpine; Part II. A Method for the Generation of Metalloenamines."

I have been employed since July 1, 1981 by Eli Lilly and Company as a medicinal chemist. I currently work in the Discovery Chemistry Research and Technologies department and my title is Research Advisor.

I have authored or co-authored 29 research papers published in scientific journals.

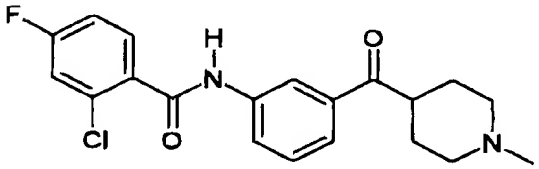
I am the inventor or co-inventor of 86 United States patents.

I further declare that I am an inventor named in the above-identified patent application Serial No. 09/890,741.

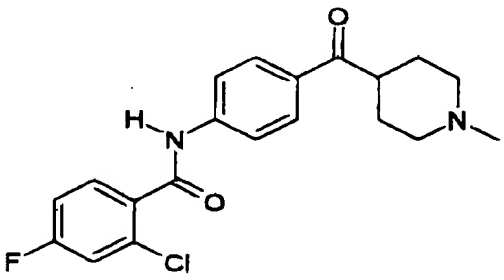
I further declare that the following experiments, demonstrating the unexpected superiority of the compounds of Formula I of the patent application having substitution at the 3-position on the benzene ring over similar compounds having substitution at the 4-position on the benzene ring were carried out under my supervision and control.

Experiment

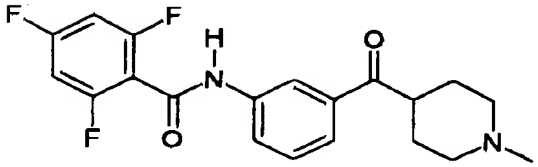
The following pairs of 3- and 4-substituted benzoylpiperidine compounds were synthesized and their affinity for the 5-HT_{1F} receptor was determined using the 5-HT_{1F} radioligand binding assay described in the patent application.



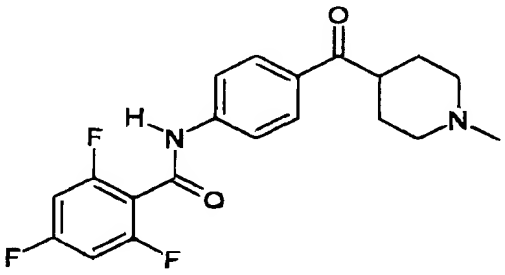
compound 1
5-HT_{1F} Ki = 1.9 nM (N=5)



compound 2
5-HT_{1F} Ki > 4600 nM (N=2)



compound 3
5-HT_{1F} Ki = 2.5 nM (N=2)



compound 4
5-HT_{1F} Ki > 4700 nM (N=2)

Results

The test compounds' affinities for the 5-HT_{1F} receptor are given in the figure above. The 3-substituted benzoylpiperidine derivatives, compounds 1 and 3, both have high affinity for the 5-HT_{1F} receptor, with Ki's of 1.9 nM and 2.5 nM, respectively. Compounds 2 and 4 are the 4-substituted benzoylpiperidine analogues of compounds 1 and 3, respectively. In

contrast to the high affinity of compounds 1 and 3, neither compound 2 nor compound 4 has appreciable affinity for the 5-HT_{1F} receptor, with Ki's for each being greater than 4600 nM. These data indicate that the position of attachment of the substituent on the phenyl ring of the benzoylpiperidine can have a very large effect on the affinity for the 5-HT_{1F} receptor and that in this case, the 3-subsituted analogues have over 1000-fold higher affinity for the 5-HT_{1F} receptor than the corresponding 4-subsituted analogues.

Conclusion

The results of the foregoing experiment clearly demonstrate that the compounds of Formula I having substitution at the 3-position on the benzene ring have an unexpectedly much higher affinity for the 5-HT_{1F} receptor than similar compounds having substitution at the 4-position on the benzene ring, which 4-substituted compounds, in fact, have very poor 5-HT_{1F} receptor binding properties.

I further declare that all statements made herein of my own knowledge are true, that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both (18 U.S.C. 1001), and may jeopardize the validity of this application or any patent issuing thereon.

John Mehnert Schaus, Ph.D.

Jan 28, 2003

DATE